

RUSSIAN STUDIES ON

Age-Associated

Physiology, Biochemistry,  
and Morphology

*Historic Description With Extensive Bibliography*

*Vladimir Nikolovich*  
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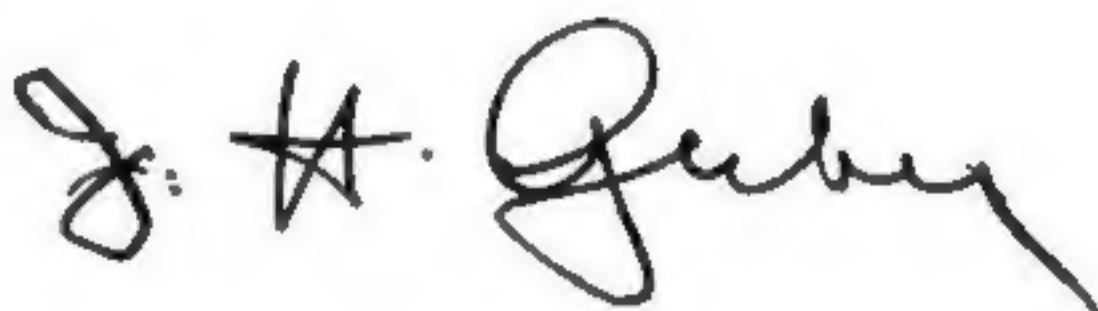
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## Foreword

PROFESSOR V. N. NIKITIN, USSR, has provided a comprehensive review of Russian studies and theories of age-associated physiology, biochemistry, and morphology spanning the years 1761 to 1958. With its almost 3,000 references it is a document of significant historical interest. For this reason it is being made available to all those engaged in aging research in this country.

Except for a few minor editorial changes and deletions, this monograph is a faithful translation from the Russian original, for which we are indebted to the staff of the Library of the National Institutes of Health.



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## I. FIRST STEPS IN THE PHYSIOLOGY OF AGING IN RUSSIA

(The period of accumulation of individual facts and initial generalizations)

The U.S.S.R. is the motherland of the physiology, biochemistry, and morphology of aging. The works of such eminent scientists as I. I. Mechnikov, M. S. Mil'man, I. P. Pavlov, A. A. Bogomolets, A. V. Palladin, N. P. Krenke, A. V. Nagorniy, and others have substantially enriched the contemporary knowledge of aging in the higher organisms. Through the work of A. V. Nagorniy and his pupils, the problem of aging and the fight for longevity led to the development of a new branch of biology (physiology), namely, age-associated physiology and biochemistry. At its distant base stands the giant figure of the founder of Russian science, M. V. Lomonosov. In his lecture "On the multiplication and preservation of the Russian people" (1761), he traced a remarkably clear picture of premature death from overexhaustion, undernourishment, epidemics, and the lack of adequate medical care among a large part of the working population of Russia in the days of serfdom.

Lomonosov angrily wrote: "All the cities must have an adequate number of doctors, medical practitioners (tr.: i.e., without foreign training), and drug stores that can supply medicines, even if only those that are fitting for our climate. All of these are not available even in one hundredth part of what is needed, and even the Russian Army is very inadequately supplied with physicians, so that the physicians do not even have time to bandage the wounded, much less examine each patient, question him in detail, give medicines, and comfort the suffering. Because of this lack of foresight, many die who could have lived."

Somewhat later, Professor S. G. Zybelin, of the Moscow University, published his "Remarks on the proper care of infants" (1775). One of the aspects of this problem of proper care that he discussed was that of striving to assure the sound biological development, health, and longevity of the population of our Motherland under the social-economic conditions of that period. Five years later, he again appeared in print with his "Remarks on how to prevent the cause of the not unimportant slow multiplication of the population." Finally, in 1797, Zybelin again returned to the problem of assuring an increase in the population and its longevity in his address "On medical means of promoting an increase in the populousness of the community."



In 1812, I. P. Kamenskiy, Professor of Anatomy, Physiology, and Forensic Medicine at the Kazan University, lectured on "The physical rearing of children and its influence on their mental and moral state" and was subsequently exiled as a free-thinker. In this lecture, he discussed the physical rearing of children as the science of "preserving their good health and eliminating whatever influences may have a harmful effect upon it." He subsequently considered the effects of temperature, food, drink, movement, "mental exercise," and emotions on the child, and on the basis of this developed the doctrine of hygiene and medical care of children.

Kamenskiy ascribes an extremely great importance to emotions, both pleasant (prolonging life) and unpleasant (shortening it), in the proper upbringing of children and longevity. Pleasant passions (joy, hope, love, competition) give rise to "unpleasant stimulation of the nervous, vascular, and muscular systems; good composition and volume of blood; a favorable physiology and good spirits. Unpleasant passions act in the opposite way." Among the unpleasant passions Kamenskiy lists fear, grief, anger, hatred, envy, and jealousy.

There is an evident similarity between the views of I. P. Kamenskiy and those of A. N. Radishchev on the rearing of children.

L. O. Vanotti, Professor of Anatomy and Physiology at Kharkov University, lectured in 1818 on the significance of public health in human longevity. The lecture was entitled "The probable curability of almost all diseases." In it, he points out that "a long and healthy life is, beyond a doubt, the most necessary and desired of the gifts for which we pray to our most gracious Providence. But there are so few who are granted this highest boon, as we learn from our everyday experience of the usual mortality rate among human beings." Vanotti advanced a view that anticipated by a half century a similar statement advanced by I. I. Mechnikov: "Life is always too short to attain the goals set for it by nature; it is interrupted violently by illnesses. . . . Extreme old age is very often nothing other than a prolonged and incurable disease."

In his lecture, Vanotti stressed the qualitative peculiarities of the organism at various stages of its chronological development: "There are changes not only in the organism's external appearance but also in its entire internal structure, even in its very essence, with the continuous formation of new organs of strength and action in it, which progressively develop and again disappear, so that at different periods of life it presents an entirely different appearance to the superficial observer."

In particular, Vanotti stressed the possibility of artificial strengthening of the regeneration phenomena in the organism, and hence of a complete restoration of health after any illness. He further emphasized the fact that "all diseases are curable, and only the physician's lack of knowledge of the cause is at fault if patients die."

In 1833, there was issued from the press a large book by Parfeniy Yengalychev entitled "Prolongation of human life. Means of attaining a healthy and happy advanced old age, of protecting the health by suitable measures, and of making use of the medicaments that are to be found almost



everywhere before our eyes according to the indications of the diseases involved, as compiled from the best Russian and foreign writers." Yengalychev stressed in particular the need for making use of the "therapeutic strength of nature," preventing disease by generally observing the correctly formulated dietetic rules, treating diseases early and rationally if they do develop, and toughening the organism by means of systematic physical exercise and exposure to fresh air, strict observance of the rules of personal hygiene, and avoidance of alcoholic beverages. It is interesting that Yengalychev regarded walking to the bath-house as an important means of preserving the health and vital tone of the organism.

In 1839, I. O. Kalenichenko lectured at Kharkov University on "Influence of the ages of human life on mental and moral powers." He was an eminent zoologist and physiologist who taught a course on human physiology at the Medical School.

In this lecture, we find the very interesting statement that "life and death exist in us at every moment; we live, and yet continually die; we die, and yet continually revive."

Kalenichenko emphasized with great force the uninterrupted changes that go on during the chronological development of all living matter: "The immeasurable expanse of vitality discovered in innumerable forms of organic nature is born, matures, and fades away with the well-known manifestations of normal mutability, demarcated into more or less distinct periods. All the members of the formative area of nature, from the smallest blade of grass to the human organism, are necessarily subject to change in all the processes of their vital activity . . ."

Russian pediatrics began to develop at an early period. Its founder was Prof. S. F. Khotovitskiy (1796-1885), of the St. Petersburg Medical-Surgical Academy. In his "Pediatrics," published in 1847, he presented a number of ideas that have been extremely important for the development of the physiology of aging. Of particular value are his statements as to the specificity (qualitative characteristics) of the human organism at various stages of ontogenesis:

"... The considerable duration of childhood is associated with the gradual development of the child organism and the approximation of the child to the adult organism, and this evidently cannot be accomplished without qualitative and quantitative changes in its structure and functions. And for this reason the child organism, in a healthy or ailing state, is startling, at first glance, in its very considerable difference from the adult organism, which does not manifest itself only in the smaller size of the organs nor only in the lesser strength of the functions characteristic of the human organism but also in the specific character of the composition of the organs and the direction of their action, healthy or ailing . . ."

The studies by S. F. Khotovitskiy constitute the initial stage of the development of the physiology of aging during this period, which amounted, in essence, to a more or less random collection of individual pieces of information on hygiene, gerontology (the study of old age), and thanatology (the study of death), and of somewhat more detailed knowledge about the normal state and

pathology of childhood and of the clever generalizations and statements that were made on the problems of macrobiotics, which were, however, based on extremely little scientific material. It was I. I. Mechnikov (1873–1916) who brought the problem of the control of premature aging and of promoting a long, happy, and fruitful life to its present scientific heights.



## II. PHYSIOLOGY OF AGING BEFORE THE OCTOBER REVOLUTION [tr.: 1917]

(Establishment of the first scientific schools and theories in  
ontophysiology)

A remarkable Russian biologist, the author (with A. O. Kovalevskiy) of evolutionary embryology and the founder of the theory of phagocytosis, I. I. Mechnikov investigated the problem of longevity for more than 40 years and established a valuable theory of aging. He published 39 experimental studies and monographs in this area, among them such fundamental and now classic works as "Studies of the nature of man" (1903-1904), "Studies of optimism" (1907), "Prolongation of life" (1912), "Forty years of searching for a rational Weltanschauung" (1913), and others.

Mechnikov expressed the remarkable thought that "human life fails half-way along its course, and our old age is a disease, which must be treated, like any other." This idea is basic to many of his investigations, which were the first to introduce the concepts of pathological and physiological aging into science. He sought to give man an opportunity to achieve a normal physiological old age, without senility or deep degradation of physical and intellectual powers. He conjectured that attainment of extreme old age would eliminate that disharmony of the nature of man which he so clearly depicted in the following words: "Our strong desire to live finds itself contradicted by the weakness of old age and the briefness of life. This is the greatest disharmony of human nature." When the organism is "used up," man accepts death as happily and peacefully as he always accepts rest and sleep after a fruitful and productive day of work. It must be noted, however, that this last vision expressed by Mechnikov is not fully justified. Even very old people do not lose their instinct to live.

In his theory of aging and death, Mechnikov combined the concept of an intoxication of the organism that continued to increase with age (attributable, to a certain extent, to a decay of the intestinal microflora) with the idea of the non-uniform sensitivity of different tissues to this intoxication. The "noble" (most valuable and delicate, tissues, especially the parenchyma of the brain and heart, kidneys and liver, are very susceptible to poisons; connective tissue, on the other hand, retains its full value and ability to multiply to advance old age. Hence the "struggle," in the aging organism, between the tissues, the growth of the connective tissue and its supplantation of the "noble" tissues, which is accompanied by a consumption of the dying cells of the nerve, muscle, and glandular tissues by macrophages that are activated during old age.



"I have formulated my view in the following manner: in senile atrophy, we always encounter one and the same picture, namely, an atrophy of the noble and specific elements of the tissues and their replacement by hypertrophied connective tissue. The nerve cells in the brain, i.e., those that serve for the highest forms of activity—mental and sensory functions and the guiding of movements, etc.—disappear and yield their place to lower elements known as neuroglia, a kind of connective tissue of the nerve centers. In the liver, connective tissue supplants the hepatic cells that play an important part in the feeding of the organism. This same tissue also invades the kidneys; it constricts the canals that are necessary to rid us of a multiplicity of harmful substances. In the ovaries and testes, the specific elements that serve for the multiplication of the species are similarly supplanted and replaced by cells of the granular layer from the connective-tissue series.

"In other words, old age is characterized by a struggle between the noble elements of the organism and the simple primary ones, a struggle that terminates in favor of the latter. Their victory is reflected in a weakening of mental powers, nutritional disturbances, impaired metabolism, and so forth.

"When I speak of a 'struggle,' I am not using a metaphor. We are concerned here with a veritable battle in the very depths of our bodies."

Mechnikov ascribed considerable importance in aging to the destruction of the brain cells by macrophages: "... in senile degeneration, an especially important role is played by the atrophy of the nerve cells with the aid of the macrophages."

In the fight against premature aging, Mechnikov recommends orthobiosis, i.e., the doctrine of the healthy and hard-working life without excesses. Also an important factor in the fight against premature aging, according to him, is the suppression of putrefactive processes in the large intestine by the use of lactic-acid bacteria (he recommended kefir, kumys, and acidophillin): "In order to render old age actually physiological, it is necessary to counteract the discomforts resulting from the development of the large intestine." "... thus, it is entirely clear that for the purpose of shortening these slow poisonings, which weaken the resistance of our noble elements and strengthen the phagocytes, we should introduce kefir, and even better, sour milk, into our dietary regimen."

Mechnikov believed that a third way to fight for a longer life was to suppress the macrophages by increasing the amounts of specific antimacrophagic immune serum. Mechnikov did not succeed in working out this control method successfully.

Mechnikov's ideas formed the basis for the investigations of a number of his pupils and successors. These ideas found a certain echo and further development in each of the great investigators in the field of longevity.

The works of I. I. Mechnikov laid the basis for the contemporary Soviet science of aging and death, and contributed to the fight for longevity. From that time on, research in this field was widespread in Russia. The first formation of almost all branches of the physiology, biochemistry, and morphology dates back to the 80's and 90's of the last century.



The comparative statistical approach to the problems of aging and the human life span first appeared in the Russian literature on ontophysiology in a study by K. A. Andreyev (1871): "On mortality tables." He set the task of "finding a correlation between the mortality rate and the various factors that influence it; in other words, of finding an analytic formula in which the mortality rate would be expressed as a function of all the factors that influence it." It is interesting that the critical age for males, i.e., the age that he regarded as most dangerous to males (the greatest percentage of deaths), was given by him as between 40 and 45 years.

Thirty-two years after this study, the prominent physical chemist P. D. Khrushchev (1903) studied in detail, by the statistical method, the causes of death at each age and the problem of the natural duration of human life.

He showed that the mortality curve was very high for early infancy, dropped by 14 years, gradually rose to the age of 71.5 years, then sank [tr.: sic], soon meeting the abscissa at 106 years. Here we find support for Mechnikov's view that ordinary old age is pathological old age and that the great majority of deaths are premature. Having established the five critical periods in human life, Khrushchev came to the conclusion that there are no "sharply detached and entirely independent ages. Life proceeds smoothly and continuously from the beginning to the end; strictly speaking, there are no individual ages but rather five special groups of causes and conditions that create life and lead to death; the majority of them act over periods of many years, others for almost the entire lifetime, but they predominate during certain years of existence, when it is especially convenient to recognize, study, and investigate them."

During the 80's and 90's of the last century, the investigations of the distinguished Russian zoologists N. A. Kholodkovskiy (1882) and V. M. Shimkevich (1893) and the eminent physiologist I. R. Tarkhanov (1891) were directed to development of theories of aging. Kholodkovskiy was particularly interested in the problem of the existence of natural death among protozoans and the genesis of death in higher animals. Shimkevich regarded aging as the result of a peculiar degeneration of the tissue cells, due to an imperfect process of karyokinesis: "It seems to me that it is in this imperfection of the process of division" (the fact that it is not possible to divide the biophores in a strictly equal manner between the daughter cells, V. N.) "that we should seek the cause of aging of organisms and degeneration of cells . . . If Nature could develop a cell with an ideally exact structure and with mathematically accurate division, it would create immortality."

Tarkhanov formulated the concept of death as the exhaustion of a hypothetical substance present in limited amounts in the fertilized ovum. This substance, bound to the nucleus, is parceled out, in the course of metazoan multiplication and differentiation, into "so many trillions and quadrillions of particles that, as a result of their endless division in the course of cell multiplication, they must attain such minimal magnitudes that they are no longer able to exert any creative force, and then they cannot overcome the damage incurred during life . . . The cause of natural death is not the wear and tear on the cells themselves but rather the progressive reduction of the ability of the cells



to create and multiply, attributable to the progressive depletion of the nucleus-forming substance . . . The number of generations of cells that can develop in the course of a whole lifetime from the fertilized egg, thanks to its original store of creative energy, also determines longevity and hence the maximum length of life that can be attained by various organisms . . . The quantity of this creative energy seems to be standardized for each species . . .” This theory, as formulated in several variations by Butschli (1882) and J. Loeb (1903, 1908), cannot be subjected to critical evaluation within the scope of this review. This has been done in an excellent fashion in a monograph by A. V. Nagorniy (1940). The basic objection to the theory is the fact that after millions of years of existence of life, this hypothetical substance would long since have been used up (in the very first generations of living matter).

During the 80's of the last century, some excellent studies appeared, written by I. M. Sechenov, on the physiology of the central nervous system. Some of them contain very extensive discussions of problems relating to the origin of the higher forms of behavior in the early ontogenesis of man. In his work entitled “For whom and how should psychology be developed?” (1873), Sechenov gives the classic definition of the tasks of materialistic psychology:

“(1) Psychology should study the history of the genesis of the individual elements of the picture.<sup>1</sup>

“(2) It should study the method by which the individual elements are joined into a continuous whole.

“(3) Finally, it should study those springs [tr.: ‘triggering mechanisms’?] that determine each new development of psychic activity after an interval.”

In other words, if we translate these expressions into scientific language:

(1) Psychology must study the history of development of feelings, concepts, thoughts, sensations, and so forth.

(2) It must then study the combinations of all these species and genera of mental activities with one another . . .

(3) Finally, it must study the reproduction of mental activity.<sup>2</sup>

“On the basis of all its content, scientific psychology cannot be anything other than a series of studies on the origin of mental activities.”<sup>3</sup>

In “Elements of thought” (1878), Sechenov indicated, one after another, the stages of the ontogenetic formation of higher nervous activity (behavior) in the child. He asserted that “in the mental life of man, only early infancy presents cases of the actual genesis of thought of ideational states from psychological products of a lower form, which do not have the character of thought. It is only here that observation reveals the existence of a period in which man does not think, and after this the ability to think gradually makes its appearance.”<sup>4</sup>

I. M. Sechenov was the first to work on the ontogenetic physiology of higher nervous activity.

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<sup>1</sup> Higher nervous activity, V. N.

<sup>2</sup> I. M. Sechenov: Collected works. 152, p. 208.

<sup>3</sup> Ibid., p. 209.

<sup>4</sup> Ibid., p. 272.

In 1884–1897, the remarkable Russian physiologist V. M. Bechterev published his studies of the characteristics of the age-associated morphology and physiology of the central nervous system. He was particularly interested in the very earliest stages of ontogenesis.

During the same period, A. N. Alelekov (1892) investigated senile changes in the functions of the nervous system. In his dissertation, he included a very detailed review of the literature (starting with 1537), but unfortunately without consideration of the contemporary need for providing bibliographic material.

This group of studies is evidence of the appearance of a new and important orientation of research, along the lines of the physiology of aging of the nervous system, which found its culminating expression in the works of I. P. Pavlov's school.

To this same period belong the classic studies of I. P. Pavlov (1895–96), who studied the causes of death of dogs that had been subjected to bilateral vagotomy. Pavlov succeeded in showing that vagotomized dogs were still capable of living. These were Pavlov's first papers on the significance of the nervous system as regards the ability of higher animals to survive. The flowering of the work of Pavlov and his pupils on senile changes in the nervous system (and also on the ontogenetic development of the cerebral cortex) came in later years.

An important place in scientific investigations must be given to the Russian teacher, anatomist, and physician P. F. Lesgaft, who concerned himself with the problems of the morphology, morphophysiology, and ontogenesis of aging in human higher nervous activity. He based his remarkable system of physical education, as well as his system of general education of the child, on his deep knowledge of his functional anatomy and psychology.

Lesgaft gives the following excellent formulation (1884) of the tasks and methods of family education (and education in general): "The whole secret of family education consists in giving the child an opportunity to develop himself, to do everything himself; the adults must not fuss with him and should not do anything for his personal comfort and pleasure but should always, from the first day of his life, treat the child as a human being, with full recognition of his personality and of the fact that this personality must remain inviolate."

The problems of education, conceived of so deeply and humanely, require a broad knowledge of the successive phases of the ontogenetic development of the child's structure and function and of the changes in the level of his mental activities. In his "Fundamentals of Theoretical Anatomy" (1905), Lesgaft gave a good deal of space to an investigation and evaluation of the morphology of aging in the child and adult. He made a particularly thorough study of the age-associated development of cardiovascular and muscle systems of man. In "Family Education of Man and its Significance" (1884–1910), Lesgaft made a deep and original analysis of the progressive development of higher nervous activity and analyzers in the child, especially in very young infants.

According to Lesgaft, "we find that according to the gradual and successive course of development of mental abilities in the normal child, his development can be broken down into the following periods.



- (1) A chaotic period, characteristic of the newborn infant.
- (2) A reflex-experimental period, usually extending to the appearance of speech, or approximately to the beginning of the second year after the child's birth.
- (3) An imitative-practical period, up to school age.
- (4) An imitative-ideational period, the school period up to the age of 20 years.
- (5) A critical-creative period, essentially that of mature adults, with some subdivisions."

This attempt to subdivide the periods of development of the human psyche had an undoubtedly progressive significance for that time.

Lesgaft gives a remarkable characterization of the early stages of development of the child's sensory organs and psyche (up to the age of 2 years):

"In the newborn infant, the higher senses are still not well enough developed for us to detect any activity associated with them; through their instrumentality, only some reflex factors receive a signal. The child gradually begins to perceive tactile and muscle sensations, taste, odor, and visual and auditory sensations. But these sensations are not yet differentiated consciously so long as the interaction of the sensations that excite the various sensory organs has not determined their conditionality. It is only then that ideas are formed from sensations. In addition to this, the child begins to distinguish the pleasant from the unpleasant: he is a smiler. This occurs before the end of the third or at the beginning of the fourth month. The infant goes from a lying to a sitting position at the beginning of the second half of the first year; he begins to crawl and look at everything that surrounds him: he is an observer. During the ninth or tenth month, the infant begins to stand on his feet; he utters some articulated sounds and grasps everything: he is a grasper. During the first half of the second year, the infant moves easily and continues to accelerate his movements: he is a runner, and in the second half of the same year he easily utters articulated sounds and masters more and more words: he is a babbler and imitates everything. It is also at this time that he begins to form his habits. Toward the end of the second year or at the beginning of the third, he isolates himself, by making a comparison, from the surrounding environment and speaks of himself in the first person as I."

At the beginning of the 90's, the studies of I. V. Troitskiy (1890-1912) and especially those of N. P. Gundobin (1891-1912) raised the development of Russian pediatrics to new heights.

Troitskiy proceeded from a recognition of the singularity of the infant organism and of its qualitative difference from the adult organism: "The infant is not a miniature edition of the adult" (A. Jacoby). He emphasized the fact that "the anatomic-physiological modifications that regularly occur in the course of growth, the sensitivity of the child organism in general and of its individual organs in particular, very different in the various periods, with respect to harmful factors, the ability to counteract these, weak at the start but gradually increasing with age: all of this, taken as a whole, gives the pathology of childhood its independent character" (I. V. Troitskiy, 1907).

Troitskiy made valuable studies of the digestion and metabolism of small children. His fundamental work is "The Study of Childhood Diseases" (1907).

One of I. V. Troitskiy's pupils, P. P. Eminent (1907-1911), made a thorough study of age-associated changes of the sphygmogram in children (from 1 to 15 years of age) and the properties of the blood platelets in the growth period of the organism and showed the marked toxicity of dyspeptic feces of year-old children.

The work of N. P. Gundobin (1891-1912) was very important in Russian pediatrics. During the seven years that he was director of the Children's Academy Clinic, Gundobin established a major scientific trend in the study of the anatomic-physiological characteristics of childhood and the peculiarities of children's diseases. He and his pupils established more than 100 papers on age-associated physiology and anatomy and on pediatrics. Gundobin generalized the results of these investigations in his excellent monograph entitled "Characteristics of Childhood. Basic Facts for the Study of Children's Diseases" (1906). Gundobin's monograph was reprinted several times in Russia and translated into foreign languages (the first German edition appeared in 1912).

Gundobin provided a firm basis for his initial view as to the qualitative singularity of the child organism: "In view of his anatomical, physiological, and chemical characteristics, the infant differs sharply from the adult human being and merits special study."

Gundobin also wrote the excellent pediatrics textbook entitled "Upbringing and Treatment of the Child up to the Age of Seven Years," which was published three times: in 1907, 1909, and 1913.

Gundobin's experimental work was directed to the study of the characteristics of the digestion, the morphology and pathology of the blood, and higher nervous activity in the child. Finally, he also wrote "General and Particular Therapy of Children's Diseases" (published in 1896, 1900, and 1907).

A further development of Russian pediatric thought appeared in the form of a two-volume monograph by N. V. Vyazemskiy entitled "Changes in the Organism during the Period of Formation" (1901), in which the author gave the results of the scientific investigations of that period in the fields of the anatomy, physiology, psychology, and pathology of the child, adolescent, and young adult (up to the age of 20 years). This book contains a detailed list of the Russian and foreign literature in this field and also presents the extensive material of Vyazemskiy's own observations, which are of considerable scientific significance.

During the 80's and 90's of the past century, the investigations of A. Ya. Danilevskiy (1881-1891) provided the first contributions to Russian age-linked biochemistry.

Danilevskiy, who may be regarded as the founder of Russian biochemistry in general, laid considerable stress, in his splendid works, on the study of proteins as the basis of the vital process. It was his opinion that "protein is the basic material for life on earth. There is no vital process in our organs in which a protein compound does not take an active part in one way or another. Protein is the instrument and carrier of our joys, sorrows, and thoughts. It also makes



our movements possible." This formulation is very close to the remarkable concept expressed by F. Engels, who described the life process as a means of existence of protein substances: "*Life is a method of existence of protein substances, and this method of existence consists essentially in a continuous renewal of the constituent chemical parts of these substances*".<sup>6</sup>

Danilevskiy confronted biochemistry with the task of studying the phylo- and ontogenetic evolution of proteins and other substances of the protoplasm: "Beyond a doubt, knowledge of the course and laws of the chemical evolution of organs, tissues, and the organism as a whole represents one of the most important links in our understanding of life on earth" (a statement of his pupil N. F. Baymakov, 1904).

Danilevskiy suggested (1886) that synthetic (plastic) processes are accomplished in the organism with the aid of special plastic enzymes. Effective functioning of these enzymes requires the action of the so-called stimulin (a specific stimulator). In ontogenesis, there is a continued expenditure of the supply of stimulin, which is laid down in the embryo and there bound to protein substances. When the protoplasm is in an active state, stimulin is dissociated from its combination with proteins and acts on the plastic enzymes, giving rise to a heightened rate of synthesis (neoformation) of proteins. Even in youth, the stimulin supply is sharply decreased, and this causes a decrease in the growth rate. With old age, the organism retains only insignificant traces of stimulin, which leads to a catastrophic lowering of the neoformation of the proteins of the protoplasm.

In essence, therefore, Danilevskiy's theory of the biochemical basis of aging is close to I. R. Tarkhanov's concept of the depletion of a hypothetical vital substance in ontogenesis and has the same fundamental defect: an acknowledgement of the formation of the vital substance in phylogenesis and a non-recognition of this process in ontogenesis. Unlike Tarkhanov, Danilevskiy suggested that stimulin can be regenerated in youth, although not in its totality.

Danilevskiy (1891) was the first to establish qualitative and quantitative differences in protein composition between young and adult animals (puppies and adult dogs).

In 1886, S. D. Kostyurin (a pupil of V. V. Pashutin) studied changes in the macro- and microstructure of the human brain with aging, and in 1890 he investigated the effects of Brown-Sequard extract from the seminal glands of the senile organism (the first steps in age-associated endocrinology).

During the period from 1900 to 1917 (up to the Great October Socialist Revolution), there was further development of Russian age-linked physiology, biochemistry, and morphology. A number of new major trends and schools arose during this period, and some of these reached their flowering after the Revolution.

The investigations of M. S. Mil'man (1900-1940) the eminent Russian histologist and one of the leading Russian ontophysiologicals, began in 1900. In the years before the Revolution, he worked principally on the characteris-

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<sup>6</sup> F. Engels: *Anti-Duhring*, 1948, p. 77.

tics of the age-linked changes in the nerve cells, especially the storage of "senile pigment" in them and the degradation of the nucleoli. Mil'man made a thorough investigation of the dynamics of the change in the weights of organs in the course of ontogenesis and found that "the organs that grow for the longest time are the lungs, heart, and arteries, the organs that supply the organism with food and also with one of the most important substances, namely, oxygen. These are followed immediately by the intestines, so that we find the same thing in the complex organism as in the simple one: the feeding surface of the body increases for the longest time, since in man and animals this is not the skin but the vessels and intestines."

It was during this same period that Mil'man formulated the first statements of his theory of aging as a process of starvation (oxygen, food) of the central parts of the cells and of the organs at a distance from the periphery. Growth, increasing the dimensions of the individual cells and worsening the conditions under which oxygen and nutrients are furnished to them and to entire organs, gives rise to a lowering of vital activity, atrophy, and destruction (death). This draft of Mil'man's theory, later worked out in detail, was first published in 1901 (*Das Wachstum und das Alters*).

A number of studies in the field of the theory of aging and death were published in 1900–1907 by the prominent zoologist and zootechnologist N. M. Kulagin.

Starting in 1912, such eminent Russian scientists as A. A. Bogomolets (1912–1946), S. I. Metal'nikov (1912–1937), M. S. Maslov (1913–1947), P. Yu. Shmidt (1915–1924) G. N. Speranskiy (1914–1948), and A. V. Palladin (starting in 1916) began almost simultaneously their investigations of physiological aging.

The flowing of the scientific creativity of almost all these scientists falls into the post-Revolutionary period; for this reason, their fundamental studies will be reported later. S. I. Metal'nikov formulated his theory of aging somewhat earlier (1912–1917).

One of the eminent zoologists who did a great deal of work on the physiology of the digestion of infusoria, S. I. Metal'nikov (1912–1937), developed in a particularly thorough fashion his view of the heterochronicity of aging of different tissues and organs. He was one of the founders of the theory of aging as the result of differentiation and specialization of the protoplasm and lowering of the vitality of the cell under the conditions to be found in higher organisms. "Progressing in one direction, the cell must necessarily regress in other directions." "... And the higher and stronger this organization as a whole, the more solid and integral this new individuality of a higher order, the greater will be the enslavement of the individual elements that enter into it (cells, V. N.). Thus, the evolution of the entire organic world progresses in two different, and as it were, opposite directions. At the same time that the complex multicellular organism gradually perfects itself and progresses on the principle of division of labor and specialization of the individual elements, i.e., cells, its components regress in many respects." (S. I. Metal'nikov, 1917). Thus, "a multicellular differentiated organization already carries within itself the embryo of future



disharmonies . . . which will strive to restore the disturbed harmonies . . . Once this harmony is disturbed anywhere, even if only very slightly, the activity of the whole is disturbed and the entire system begins to be destroyed."

Extreme differentiation, connected with a loss of the cells' ability to divide and of the protoplasm's to be restored, is considered by S. I. Metal'nikov as also explaining the loss of the ability to regenerate among higher animals. This loss leads to death: "If man possessed the same ability to regenerate his amputated extremities or his head that we find in many worms and insects, if he could restore his damaged intestine as do holothurians, then, of course, neither death nor old age would be terrible to him" (1917).

S. I. Metal'nikov also wrote such fundamental works as "The Problem of Immortality in Contemporary Biology" and "La Lutte contre la Mort" (1937).

### III. THE POST-REVOLUTIONARY PERIOD OF DEVELOPMENT OF SOVIET AGE-ASSOCIATED PHYSIOLOGY

(Its formation as a science and the establishment of the more prominent scientific schools)

The greatest development of the research of Russian scientists in the fields of age-associated physiology, biochemistry, and morphology has been achieved since the Great October Socialist Revolution. During this period, the struggle for a long and happy human life, with retention of the ability to work, became the task of the State and assumed importance for the entire people. The structure of the socialist society creates the social prerequisites for success in this struggle: a radical improvement in the life and environment of the workers, a maximum concern for their work and rest, a great expansion of medical services, State care for the aged, care for mothers and children, construction of a network of sanatoria and rest houses, large-scale development of physical culture and sports, etc.

Soviet science, which was provided with extremely favorable conditions for its growth, found itself confronted with one of the most pressing of problems: the development of the necessary prerequisites for longevity. This has been described in an excellent fashion in the classic work on Soviet ontophysiology written by A. V. Nagorniy (1940): "And now, when the last shadows of the social conditions that shortened life are fading into the past, when the earth is ceasing to be 'a world of groans and tears,' Soviet science is confronted with the great task of overcoming those biological disharmonies that interfere with longevity and that, long before death, condemn man to senile weakness and senile degradation."

In the development of Soviet ontophysiology, there has been an organic fusion of both those trends and schools that had arisen before the October Revolution and the new scientific schools and trends. Out of the uncoordinated individual investigations and efforts of the narrow scientific communities of post-Revolutionary ontophysiology, there developed a powerful, rapidly growing outgrowth of the science with many large schools and trends.

A remarkable contribution to the problems of age-linked physiology was made by I. P. Pavlov (1908-1936) and many of his pupils. The creation of an integral science of higher nervous activity inevitably necessitated an expansion of research on the phylogeny and ontogeny of conditioned bonds in the animal



world. From this there arose two extremely fruitful trends in the Pavlovian studies: on the comparative and on the age-associated physiology of temporary bonds.

I. P. Pavlov later made a special point of directing the research of a number of his pupils to the problems of the age-linked physiology of the central nervous system. These investigations were carried out along two lines:

- (a) a study of the genesis and early forms of conditioned-reflex activity;
- (b) a study of the characteristics of higher nervous activity in old age.

The first line was represented by the works of many investigators of the Pavlovian school. The embryogenesis and early postembryogenesis of reflex activity were first studied and are still being investigated by A. A. Volokhov (1938–1951) and his coworkers (G. A. Obraztsova, Ye. P. Stakalich), I. A. Arshavskiy (1936–1956) and his coworkers (E. I. Arshavskaya, V. D. Rozanova, S. I. Yenikeyeva), and others.

According to A. A. Volokhov, "the study of the characteristics of nervous activity in the embryonic and early postnatal periods make it possible for us to understand the course of its historical genesis and from this to clarify those complex phenomena of nerve functions that take place in the highly developed adult organism" (p. 267, 1953). The general picture of the early ontogenesis of brain activity is characterized by A. A. Volokhov in the following words: "On the basis of the studies that have been made, we can come to the conclusion that the development of reflex activity in ontogenesis is an extremely complex matter. Arising during the early stages of ontogenesis in the form of individual local reflexes, this activity quickly becomes more complicated and transforms itself into generalized forms of reflex reactions. Later on, we observe the conversion of the generalized reactions into specialized reflex acts, which progressively reach that degree of maturity which is characteristic of the adult animal." (See collection: "Teachings of I. P. Pavlov in Theoretical and Practical Medicine," Moscow, Medgiz, p. 287, 1953).

I. A. Arshavskiy's studies later developed into a very interesting trend in ontophysiology, revealing the mechanisms of the age-associated formation of the fundamental nerve processes (according to the orientation of the school of N. Ye. Vvedenskiy and A. A. Ukhtomskiy) and of the regions of the visceral nervous system. Arshavskiy and his pupils are to be credited with more than 150 experimental studies, which made a substantial contribution to the development of Soviet age-associated physiology and in particular to that of the ontophysiology of the nervous system.

The first investigations of the Pavlovian school on the early ontogenesis of higher nervous activity in man were the studies of N. I. Krasnogorskiy on the characteristics of the formation of conditioned reflexes in children (1907–1908). I. P. Pavlov strongly approved of them: "Your experiments are very interesting. It is natural that after analyzing conditioned reflexes in animals we should wish to make an attempt to compare our findings with the phenomena of our internal world. Then these experiments must be reproduced on human beings, and first of all on children. And when a similarity has been established accurately and scientifically, it is then time to compare the phenomena of the

internal and external worlds. Thus, your experiments seem to me to be both necessary and important." (Complete Collected Works, vol. 1, p. 396, 1940).

In reality, the investigations of I. S. Tsitovich (1911), who experimented on newborn puppies and showed that natural conditioned reflexes appear as a result (derivative) of the experiences of life, belong to the very earliest investigations of Pavlovian physiology on the ontogenesis of higher nervous activity.

Higher nervous activity of children was studied in detail by N. I. Krasnogorskiy (1907–1954), A. G. Ivanov-Smolenskiy (1929–1956), N. M. Shchelovanov (1925–1930), N. I. Kasatkin (1935–1955), and other investigators.

A number of Pavlov's pupils investigated the formation of conditioned-reflex activity in the early ontogenesis of animals. The studies were performed on puppies (F. P. Mayorov, 1929–1933), calves (F. S. Pavlov, 1938), guinea pigs (K. L. Golubeva, 1939–1949), and young birds (L. S. Gorsheleva, 1936).

All the investigators showed that in early ontogenesis the conditioned-reflex activity gradually assumes the full value and high functional formation and vigor characteristic of the adult individuals of the species, with a definite sequence for the exciting and inhibiting processes. In very young animals, conditioned reflexes are formed more slowly and inhibition develops more slowly than in the adults. The inhibitory functions of the cortex generally lag somewhat behind the excitation in development. The concentration of the nerve processes is also still very weak at the beginning of ontogenesis, and there is, to the contrary, a predominance of irradiation. Formation of differentiation in very young animals gives rise to subsequent inhibition and sleep, whereas differentiation in older animals is accompanied by positive induction, as a result of the concentration processes that have been formed.

The great importance of the work of I. P. Pavlov's school on the early development of higher nervous activity in animals, and particularly in man, was also emphasized by N. I. Krasnogorskiy: "Thus, strictly physiological study of cerebral activity in children has become a new and very important subject for pediatric studies. This has enriched pediatrics with knowledge of the work of the higher areas of the brain in children during various age periods and has provided a substantial basis for the further study and physiological understanding of the most complex brain processes." (Papers on the Study of the Higher Nervous Activity of Man and Animals, vol. 1, p. 311, 1954.)

In the years that followed, I. P. Pavlov gave a great deal of attention to the study of the characteristics of higher nervous activity in late ontogenesis. As early as 1912, A. V. Tonkikh carried on investigations along these lines on conditioned reflexes in old dogs. It was already clear at that time that new conditioned reflexes are formed toward the end of life with very great difficulty and are characterized by their extremely temporary character and lability. Further work along these lines was done by L. A. Andreyev (1924), D. A. Biryukov (1929), M. Ya. Mikhel'son (1934), N. A. Podkopayev (1938), D. I. Soloveychik (1932–1938), A. I. Pavlov (1938), G. V. Fol'bort and A. V. Semernina (1940), N. K. Zol'nikova (1940), M. K. Petrova (1938–1953), M. A. Usiyevich (1938–1953), and others.



The problems of the age-linked and comparative physiology of the central nervous system were of great interest to such prominent representatives of Pavlovian physiology as L. A. Orbeli (1933-1955) and K. M. Bykov (1946-1949),

I. P. Pavlov, on the basis of the "mean" results of many investigations noted a "natural decline of the stimulation process" in old age. The inhibition process suffers to an even greater extent: "With aging, there is first a weakening of the inhibition process, and then the mobility of the nerve process suffers, with an increase in inertia." He formulated his views as to senile changes in higher nervous activity in more detail, in the following manner: "... On the basis of all the material at our disposal, we can say that the inhibition process is the first to succumb to old age, and after this, it would appear that the mobility of the nervous processes is affected. This is evident from the fact that a large percentage of our aging dogs ceased to tolerate the previous more complex conditioned-reflex system. The responses become chaotic, the effects fluctuate in an entirely irregular fashion, and good results can be obtained only by simplifying the scheme. I think that this can very legitimately be ascribed to the fact that mobility decreases with the years. If we have a distinct effect in a large system, this means that one stimulus does not interfere with another and does not spread its effect to the next nerve process. When a nerve process is delayed, however, the remaining traces of each stimulus become prolonged and influence the succeeding ones, i.e., we have a chaotic state and confusion." (Pavlovian Environments, vol. 2, pp. 121-122, Izd-vo AN SSSR, M.-L., 1949).

In addition to this, I. P. Pavlov's pupils established cases of exceptionally long maintenance of full higher nervous activity (as, for example, in the case of the dog Postrel in Fedorov's experiments.)

In her extensive experiments on the nervous systems of dogs aging under various conditions of functional stress, M. K. Petrova established the very great significance of the preservation of the nervous system in longevity. As a result of this, Petrova is inclined to regard a progressive weakening of the nervous system as the principal cause of the age-associated changes in the organism: "... In our dogs, we were able to observe both normal physiological and pathological old age. Our experimental findings indicate that the major and leading role in the process of aging of the organism is played by the central nervous system, and particularly by the cerebral cortex and the other systems associated with it." (On the Role of the Functionally Weakened Cerebral Cortex in the Genesis of Various Pathological Processes in the Organism, Medgiz, L., p. 70, 1946).

Having indicated that there can be no doubt of the great significance of the nervous system for the organism as a whole and for its age-linked changes in particular, A. V. Nagorniy (1954) suggests that it may indeed be a major factor in longevity. "It can be shown that of all the systems of the intact organism (in the absence, of course, of pathological manifestations), the most stable, the most plastic, the most intensely functioning and longest-lived is the system of the cerebral hemispheres" (p. 26).

Comparative and age-associated biochemistry and physiology, particularly the age-associated changes in the gradient of intestinal automatism, the physiology of the skeletal musculature, the trophic influence of the nervous system, and a number of problems of embryo-chemistry have been studied (and are still being studied) by Kh. S. Koshtoyants (1931–1954) and his coworkers (R. L. Mitropolitanskaya, A. M. Ryabinovskaya, G. A. Buznikov, V. A. Muzikantov, and others). In this connection, they have paid particular attention to the comparative physiology and biochemistry of amphibians, fish, and some invertebrates (*Bombyx mori*).

M. S. Mil'man's investigations (1900–1940) were of special interest in the field of Russian age-linked physiology. On the basis of a large group of anatomical and histological findings, Mil'man advanced his theory of aging as being the result of atrophy from starvation (food, oxygen, and neurotic). According to Mil'man, starvation of cells (and especially of their central nuclei) is the result of their growth. In the cell, "the position of the peripheral particles [tr.: molecules?] is more favorable: they can receive more substances for assimilation than can the central ones. The result of this is an unequal growth of the external and internal parts. . . . The protoplasm is more favorably situated with respect to the surface, i.e., to the source of food, than is the nucleus, and for this reason the latter, in the course of growth, reveals signs of starvation and atrophy earlier than does the protoplasm."

The growth of cells brings with it, according to Mil'man, a whole series of "bioreductive processes": (a) changes in their size and shape; (b) changes in structure and chemical composition; (c) displacement of the protoplasm by metaplasmatic formations; (d) death of the cells.

"Consequently, the growth of the cells gives rise not only mechanically to arrest and regression of growth but also chemically: nutritional deficiencies and autointoxication, accumulating, bring about the death of the cells of the organism . . . The organ cannot atrophy if it is fed properly" (M. S. Mil'man).

In the multicellular organism, the conditions of tissue nutrition are still worse, and especially those of its centrally situated cell groups: "With an increase in the number of cells, the vessels are unable to reach every cell, for the simple reason that they can grow only in two spatial directions, whereas the mass of the cell grows in three directions."

Hence Mil'man regards as bioreductive phenomena the differentiation of nuclei in cells, cell division, tissue differentiation, and the growth of extracellular masses and connective tissue, and it is to these that he ascribes the age-linked arrest of the organism's growth and its subsequent death. ". . . Aging begins very early, even with the first cell division, with the first manifestation of life. The concept of life also includes that of aging . . . In its first multiplication, the cell creates an obstacle to its nutrition. With each division, these obstacles increase. Growth depends on nutrition, and continuously digs its own grave."

"The severe worsening of the nervous system's nutrition with increasing age leads to its premature atrophy, and this brings with it the early death of the entire organism as a result of impaired nutrition of the tissues." Although the first cause of starvation of the cells is to be found in the conditions of its growth,



and the changes in the nervous system are actually the consequences of changes in the cells of the organism, we find that in old age the role of the nervous system becomes the major one, and atrophy from aging is of neurotrophic origin" (M. S. Mil'man). [Tr.: This quotation has an end but no beginning.]

The significance of Mil'man's work is to be found above all in the accumulation of a great deal of anatomical-histological material on the processes of senile atrophy and dystrophy. His theory of aging, although characterized by its consistency, is constructed in an extremely one-sided manner and does not cover the real wealth of the relationships between growth, nutrition, and tissue differentiation in the organism. We can scarcely regard the dimensions of the cells as the factor that limits their nutrition; as a compensation, the protoplasm becomes more penetrable. It is entirely impossible to explain cell and tissue differentiation by nutritional deficiency. The fact that the tissues of higher animals are supplied by the circulatory system with capillaries does not impair but rather improves considerably the supply of oxygen and nutrients to their tissues, and this is indicated by the higher energy metabolism levels of mammals and birds as compared with the lower vertebrates, although their body masses fluctuate within narrow limits. Senile changes in the microstructure of nerve tissue are not greater but even smaller than those of many other tissues.

In view of all of this, we cannot express our agreement with the one-sided theory of the aging of organisms advanced by M. S. Mil'man, although we do commend his extensive research activities. Grasping only the one aspect of growth to which his simplified concept applied, Mil'man saw the growth and development of organisms only as regressive (bioreductive) processes. The phenomena of biological progress do not fit into Mil'man's concept at all.

During the Twenties, in addition to the echoes of A. Steinach's and S. Voronoff's hormonal theories of aging (1920 and 1921, respectively) that spread into the Russian literature, there appeared some new views as to the causes of aging in higher organisms. An unusual variation of the theory of the lack of vitality of the somatic cells (in contra-distinction to the full vitality and potential immortality of the germ cells) was developed by V. Krashennnikov (1924). He believed that the somatic cells receive an insufficient supply of certain substances that are important for their vital activity at the very time of their formation.

"The somatic cell at its very birth from the germ cell already differs sharply in its morphological structure from the germinal elements. The characteristics of the internal nature of the somatic cell determine its future fate and its specific dependence on the organism as a whole, as well as its limited existence.

"We suggest that the somatic cells, at their very birth from the germ cells, receive a definite and limited store of vital energy corresponding approximately to the time needed for the growth of the sexual elements" (V. Ye. Krashennnikov, 1924). In addition to this, for their entire life they systematically supply the germ cells with special substances that are of great genetic importance. All of this leads, at the end of ontogenesis, to a sharp decrease in the biological potential of the somatic cells and to their death.

Thus, Krashennnikov assigns to the somatic cells the role of "suppliers" of the sexual elements, so that those that are still capable of growth during the first period of life can still not only supply valuable substances to the germ cells but also rapidly synthesize its own protoplasm. During the second period of ontogenesis, there is an ever-increasing progressive attrition of the somatic cells.

The groundlessness of such a division of the cells of the body into immortal germ elements and mortal somatic cells scarcely needs to be demonstrated. According to A. V. Nagorniy, "we need only point out that if this were actually so, castrated animals would have to be immortal, whereas the facts indicate that, on the contrary, the aging and death of the soma is sometimes even accelerated after castration" (1940).

A number of studies were published by B. M. Zavadovskiy (1922-1936) and M. M. Zavadovskiy (1924-1941) from the viewpoint of a special modification of the hormonal theory of aging. M. M. Zavadovskiy regards the age-linked development of organisms as a process of prolonged morphogenesis, determined at each age by the substantial shifts in the composition and amounts of the hormones that are produced. "Despite the view, widespread among physicians and physiologists, that treats aging as a disease, and in recent times, particularly in connection with Steinach's work, as a disturbance of the 'normal' relationships in the incretory system of glands, I regard aging as a natural and inevitable finale of form development . . .

"The onset of old age must be characterized as a natural change in the activity of the incretory glands, comparable to that which, as we know, takes place when adolescence sets in during youth, when the activity of the thymus is exhausted and the gonads begin to function" (M. M. Zavadovskiy, 1924).

"... As a biologist, I could characterize our approach to the problem of aging as a morphogenetic one. It regards the phenomena of aging as the result of the normal, regular, inevitable course of development of the organism, the direction of which is determined by the incretory glands" (1924).

The concept of the hormonal dependence of aging was later defended by N. A. Shereshevskiy (1936-1940) and S. S. Khzlatov (1940). Shereshevskiy here regarded aging as being largely a manifestation of insufficiency of the thyroid gland.

That an important role is played by the age-linked changes in the glands of internal secretion in the processes of development and aging of the organism can scarcely be denied. In ontogenesis, there are substantial changes in the system of the endocrine glands; the susceptibility of the tissues to hormones also changes.

In addition to this, this concept clearly underestimates the role of the nervous system in the ontogenesis of higher organisms. The most important objection to the hormonal theories of aging is the absence in them of any answer to a major question: Why do the glands of internal secretion themselves age (or, in general, change with age)? It is evident that it is in the age-linked changes in all tissues of the organism, including those of the glands of internal secretion, that the deep-seated general causes are to be found. These factors are not touched upon by the hormonal theories of aging.



A. A. Bogdanov (1927) attempted to develop a theory of aging based on the fact that the differentiation of the organism has a negative side, leading to a contradiction in its systems. "The strength of the organism lies in the exact coordination of its parts, in the strict correspondence of the individual mutually connected functions. This correspondence is maintained during the continuing growth of the tectological differences, but not to an unlimited degree: a moment comes when it can no longer be maintained completely and begins to regress. Parts of the whole become . . . so different that they diverge both as regards the very tempo of life and as regards the strength of their relative resistance to the environment. And this inevitably leads to a disorganization, whether slower or faster, that is determined by the sum of the conditions."

Bogdanov derived this theory of the "deterioration" of the organism with aging from the idealistic principles, developed by him, of so-called tectology (a variety of empiriomonism). In it there is no scientific basis for what he postulated as an abstract contradiction between the development of the parts and units of the integral animal organism. Of somewhat greater interest are his attempts to prolong life by systematic blood transfusions. The interpretation of the blood-transfusion problem from a broader viewpoint as a means of heightening tissue tone was successfully developed by A. A. Bogomolet's school (the appearance of the so-called "colloidoclasia") and is still being studied today. The explanation of the tonicizing ("rejuvenating") action of transfused blood is given by Bogdanov in a very peculiar manner:

"To change the blood means to change the internal environment of the organism, the basic conditions of the vital activity of its cells . . .", for "foreign blood presents different relationships, different deficiencies and surpluses; it may even contain elements that are entirely absent from the blood in question. To the extent that the lack of coincidence of the deficiencies and excesses when the bloods are mixed must necessarily equalize them to a certain degree, to the extent that the vital environment becomes more harmonious, to the extent that new elements are introduced, it becomes enriched. Consequently, we find that when the choice is successful, this process is favorable to the life of cells and tissues. It may lead to an improvement of their functions, and this then in its turn has a favorable effect upon the blood, which receives material from them, as well as on its composition and properties, and even on the velocity and regularity of its circulation, and this indicates a further improvement of the internal environment."

According to Bogdanov, the transfusion of blood in higher animals is somewhat suggestive of conjugation in protozoa. Both the one and the other leads to a heightening of the biological potential of organisms. Despite his primitive notion of the character of the biological action of blood transfusion, the efforts for expansion of blood transfusion programs in the USSR and Bogdanov's establishment of a blood transfusion institute in Moscow (1926) have doubtless been of great importance for medicine and biology.

A Bogdanov died while performing one of his blood-transfusion experiments on himself.

A considerably more valuable concept of the nature of the tonicizing action of blood transfusion was given by A. A. Bogomolets (1932). He advanced the extremely interesting theory of colloidoclasia, which appeared to be the basis for the concept of the "rejuvenating" action of blood transfusion. Specifically, the introduction into the recipient organism of several proteins from the donor's blood that differ in their physical-chemical (electrocolloidal) properties gives rise to peculiar "electro-colloidal storms" (colloidoclastic shock). In this condition, there is a precipitation and automatic elimination of proteins from the protoplasm, chiefly of the older ones with lowered colloidal stability, and it, having been freed from them, is rejuvenated somewhat.

"We have already spoken of the fact that aging of the protoplasm of cells occurs as a result of a 'maturation' of the cellular colloids and micelloids and the conversion of these into precipitates and flocculates, forming biologically inert inclusions and depressing the vital activity of the cells. The majority of these flocculates are already incapable of redispersion. They have not yet, however, reached (and can never reach) those degrees of coagulation that are necessary for them to be destroyed by the intracellular enzymes. It would appear that we have here an analogy with the processes of digestion of food: the colloids and micelloids of milk undergo digestion by the digestive enzymes only after they have been coagulated. Blood transfusion provides us with a means of freeing the cell, by means of colloidoclasia, from the products of the aging of the protoplasm with which it is littered." (A. A. Bogomolets, 1940).

Over a period of many years (1912-1946), Bogomolets worked on the problems of age-associated physiology and founded in this area (aside from his other scientific services) a very prominent scientific school. Regardless of the extent to which some of his theoretical views may or may not be regarded as well-substantiated, he did have a notable role in the development of Russian physiology and pathophysiology of aging and the search for means of prolonging life. Bogomolets did a very great deal for the organizational unification and strengthening of all the principal laboratories that were working on behalf of human longevity in the USSR.

The starting point for the theory of aging advanced by Bogomolets is to be found in his idea of the extremely great significance of the connective tissue system in the organism. This system represents a special "root" of the organism, determining the extent to which the other tissues are supplied with oxygen, nutrient substances, and hormones and their excretion of carbon dioxide and other waste products. The connective tissue is an intermediary between the blood and all other tissues. Its aging begins earlier than that of other tissues and is of very great significance as regards the general aging of the organism.

"My viewpoint on the significance of the activity of the physiological system of the connective tissue for the longevity of the organism is exactly opposite to that of Mechnikov. It is my opinion that the aging of the organism begins precisely with the connective tissue. The organism is as old as its connective tissue. By no means is the connective tissue merely the elastic skeleton of the organism. I believe that the connective tissue with its diverse cellular elements is the physiological system of the organism that performs the extremely impor-



tant trophic functions, that it constitutes, in its way, the root of the organism, since it is through it and with its active participation that the substances necessary for their vital activity reach the parenchymal cells from the blood. The type of the connective tissue determines, to a considerable extent, the constitution of the organism. As early as 1924, I designated four basic types of constitution, as determined by the character of the connective tissue: pasty, fibrotic, lymphomatous, and asthenic." (A. A. Bogomolets, 1940).

The changes in the connective tissue with aging (like those in the other tissues of the organism) are based, according to Bogomolets, on the biological hysteresis of its colloids: "... The hysteresis of the connective tissue, the aging of its colloids, their thickening and condensation, their loss of water (senile desiccation of colloids), the lowering of their capillary activity, the qualitative and quantitative changes in the electrical charges of the cellular (perhaps also extracellular, V. N.) micelles of the connective tissue: all of these factors affect in a very substantial fashion the general state of the organism, the nutrition of its tissues, and its overall physiological activity" (1940).

According to Bogomolets, there is an ever increasing accumulation of aging, partially coagulated, colloidal (largely protein) particles [tr.: molecules?] in the tissues of the organism. They are unable, however, to undergo autolytic removal (autodigestion), since the degree of change in the aging protein particles, their denaturation, is still insufficient for them to become accessible to autolytic enzymes. The colloidoclastic "electrical storm" comes to the aid of the autolytic enzymes; by this means, the aged protein particles are denatured to a sufficient degree to enable them readily to fall prey to the autolytic enzymes. "It would appear that, under the influence of colloidoclasia, coagulation of the least stable 'senescent' micelles takes place and is followed by their enzymatic splitting, with the formation of autocatalysts, substances of the type of Carrel's proteases, which manifest a stimulating action on the vital activity of the cell" (A. A. Bogomolets, 1940).

Starting with the hypothesis that the tempo of aging of the connective tissue outstrips considerably that of the corresponding processes in other tissues, Bogomolets suggested that stimulating doses of the so-called antireticular cytotoxic serum (ACS) be used. The latter is obtained in response to the injection, into a donor animal, of serum from three varieties of "physiologically active connective tissue": bone marrow, spleen, and liver. Bogomolets developed a method for determining the titer of this serum and began to use it as a means of stimulating ("rejuvenating") the corresponding types of connective tissue in the aging organism.

Bogomolets compared the two means of "rejuvenation" (blood transfusion and administration of ACS) in the essence of their effects on tissues. In both cases, electrical storms in the protoplasm play a part, ridding the protoplasm of its aged and inert elements. Only in the second case is the action localized selectively in the connective tissue.

Bogomolets asserted that "study of the stimulating effect of our antireticular cytotoxic serum has confirmed the varied and important significance of the physiological system of the connective tissue. Stimulation of its functions in-

creases the level of immune substances in the blood, increases the resistance of the organism to infection, . . . and heightens the organism's resistance to cancer by promoting the absorption of fairly large neoplastic metastases and restoring the cancerolytic properties of the serum in cancer patients . . ." (1940).

Unfortunately, use of ACS as a means of heightening the potential of the organism in old age and prolonging life has not yet given highly encouraging results.

In addition to stimulation of the connective tissue, Bogomolets also sought to discover immunobiological ways of reactivating other tissues: "It may be that it will also be possible to carry out Mechnikov's idea, to the effect that it will some day be possible, by the use of specific cytotoxins, to activate the functions of the parenchymal cells and thereby to combat their premature attrition" (1940).

Two of Bogomolets's pupils (N. B. Medvedeva and N. D. Yudina) reported the stimulating ("rejuvenating") action of hemolytic serum on the proteins and cellular composition of the blood.

Of particular interest are the extensive biochemical, physiological, and clinical studies of very aged persons that were conducted by some of Bogomolets' pupils (I. V. Bazilevich, I. M. Turovets, and L. I. Pravlina, B. V. Krayukhin and N. M. Shcherbakov, R. B. Gragerova, and others (1939-1940)). On the basis of these observations, Bogomolets advanced the notion of the harmonic depression of functions in persons of very advanced old age, in contradistinction to the disharmonic processes of pathological old age.

Substantial contributions to the development of the physiology of aging were made by the investigations of some of Bogomolets' pupils: R. Ye. Kavetskiy (1939-1947), N. N. Sirotinin (1934-1951), N. B. Medvedeva (1937-1950), and others.

In Bogomolets' theory of aging, we cannot fail to note a one-sided emphasis on the exceptionally important role of the connective tissue ("the root of life") in the processes of the age-linked development of the organism and especially in the processes of its aging. We can scarcely agree with this exaggeration of the significance of the connective tissue. In Bogomolets' statements, this is connected with an understatement of the importance of the age-linked changes in other tissues, especially the nerves, and in the system of the glands of internal secretion. I. I. Mechnikov's original concept of the spreading of a number of forms of connective tissue in old age cannot be regarded as disproved.

And aside from this, the totality of the studies by Bogomolets, the extremely important factual data obtained by him and by his pupils, the various features of his teachings on colloidoclasia and the harmonic depression of functions in the very aged, his efforts to unite the uncoordinated scientific forces around the struggle for longevity: all of this has found its lasting place in the basic foundations of Russian age-associated physiology.

A large series of studies by I. I. Shmal'gauzen (1926-1938) have been devoted to the problems of growth mechanisms. On the basis of a very large number of experimental findings, he proposed his widely used growth formula and introduced into scientific practice the concept of the growth constant ( $k = C_v t$ ).



He showed that in higher animals the decrease in the rate of growth is inversely proportional to the time that has elapsed since the beginning of development. According to Shmal'gauzen, the reduction of the rate of growth is the principal determinant of the onset of the processes of attrition of tissues and the death of the organism.

Shmal'gauzen distinguishes four factors that determine the growth of organisms: a) the growth (increase in the mass) of the cells; b) the growth of undifferentiated tissues as a result of the multiplication of cells; c) the growth of differentiated cells of tissues; d) the increase in the apoplasm (metaplasma) [tr.: deutoplasm?]

He assigns a leading part in the cessation of growth and in the weakening of the autoregeneration of the protoplasm to a decrease in the mass of the undifferentiated cells in the organism. Differentiation of the cells leads to a cessation of their growth, which is as exponential in the early period of embryogenesis as it is in some bacterial cultures. In embryos "in the period of intense growth, the phenomena of differentiation are in the background, while during the period of intense differentiation growth is inhibited" (I. I. Shmal'gauzen, 1936).

In the multicellular organism, the age-associated lowering of the growth rate is determined largely by the decrease in the mass of the undifferentiated tissue elements. Undifferentiated cells continue to grow as rapidly (with the same growth constant) as in early ontogenesis. Hence, "the relative mass of indifferent cells with exponential growth decreases in inverse proportion to its age. We have here, to be sure, the entire substance of our growth law, which could be designated, with equal success, as the law of gradual differentiation of the organism" (I. I. Shmal'gauzen, 1936).

On the basis of this concept of the mechanisms of growth and its relationship to differentiation, Shmal'gauzen developed his theory of aging. One of the fundamentals of this theory is a recognition of the fact that aging and death are regarded as the result of the increasing differentiation of the tissues (cells).

In addition to this, and contrary to the view of M. S. Mil'man, Shmal'gauzen must be aware that specialization of cells not only increases their functional capabilities but also increases their life span (vital stability) substantially, as well as the integral system of the organism. "Specialization of the somatic cells of higher animals is connected with a more nearly perfect accomplishment of certain fixed functions, and in the exact coordination of the activity of the individual cells and various organs of a complex organism it assures the best conditions for their existence and we should not be surprised, therefore, that this specialization leads to a considerable increase in the life span of the individual cells. In higher animals, this life span of the more specialized and therefore unchanging cells (such as those of the nervous system, for example) is determined by the life of the whole individual i.e., it is measured in years, decades, and even centuries. The stability of the somatic cells has been increased considerably as a result of their specialization, and the most stable of these are always the most specialized nerve and muscle cells" (I. I. Shmal'gauzen, 1926).

Strictly speaking, what is it that limits the vital activity of the individual, already specialized, cells of the highly organized organism? To this question, Shmal'gauzen gives the following answer: "We believe the cause of death to be . . . the limitation of growth. The genesis of death is connected with the progressive development of a stable higher individuality of limited dimensions and strictly determinate shape with a fully harmonious relationship of the parts. In all complex animals, there is some internal apparatus that establishes the limits of growth and is passed on to the next generation, just like the other signs of organization. This apparatus, at the same time, also limits life to certain norms, since a limitation of growth is a limitation of the assimilative activities, without which it is not possible to have a complete restoration of functional damage. We designate incomplete restoration as attrition" (I. I. Shmal'gauzen, 1926).

The nature of this internal apparatus is not sufficiently clear. In this connection, Shmal'gauzen writes as follows: "This internal apparatus may be intracellular—as, for example, in the form of a well known supply of enzymes, which are used up in the course of successive divisions, and may be extracellular in the form of the specific hormones that inhibit the cell division that leads to an increase in the dimensions of the body in animals with limited growth" (1938).

Shmal'gauzen did a great deal for the study of the characteristics of growth of bacterial cultures and higher organisms and rightly stressed the significance of the increasing differentiation of the cells in the lowering of the tempo of growth and multiplication of the cells. He also stressed (together with G. S. Maynot) (1926) the significance of differentiation in the process of lowering the autoregeneration of protoplasm during the first periods of ontogenesis.

There are, however, some very substantial shortcomings in the concept of aging developed by I. I. Shmal'gauzen. First of all, we cannot agree with the statement that the growth rate of indifferent cells remains uniform during the entire course of ontogenesis. Moreover, the very existence of indifferent cells that are qualitatively identical at all ages is doubtful.

Furthermore, Shmal'gauzen's idea of "internal factors" that determine the duration of the life of the specialized cells is at least insufficient. In the first place, as has already been shown earlier (in our examination of I. R. Tarkhanov's theory), any theories that involve an expenditure of vital forces, enzymes, vital substances, and so forth, that are initially stored in them are clearly unsound. In the second place, although we cannot deny the very considerable significance of the age-linked changes in hormonal influences in the organisms of higher animals, the processes of aging ripen in all tissues without exception, i.e., also in the tissues of the glands of internal secretion, and for this reason the causes of aging cannot be sought only in a change in the formation of one or another hormone or even all the hormones as a group.

The prominent Russian physicist P. P. Lazarev (1928–1938) made a very original contribution to the development of the science of aging. Specifically, he studied the rate of the age-associated decline of the sensitivity of a number of analyzers (of sensory organs). In particular, he studied the mechanisms of the weakening of optic sensitivity with old age. Having established the rate at



which this sensitivity drops in elderly persons from 60 to 80 years of age, Lazarev extrapolated this curve further and found that it drops to zero (to the level of the axis of abscissae) for an age of 120–150 years. In other words, the sensitivity of the nervous system disappears completely at this extreme age.

This gave further physiological evidence that the normal duration of human life should exceed a hundred years.

After N. P. Gundobin, the problems of the physiology and pathology of childhood were further investigated by M. S. Maslov (1913–1947).

A number of studies on the characteristics of metabolism in early childhood were made by N. F. Tolkachevskaya (1947–1955) and her co-workers.

In addition to age-associated physiology, there has been an ever broadening investigation of age-associated biochemistry, beginning with A. Ya. Danilevskiy. The need of such investigations was formulated in a program paper by V. S. Gulevich entitled "Significance and course of development of comparative biological chemistry of animals" (1933). In it, Gulevich speaks, first of all, of the timeliness of the establishment of this new branch of science: "It would appear somewhat strange to speak of the significance of a non-existent science, but the time has now come when comparative biological chemistry must enter the fraternity of the other disciplines and when we must consider, along general lines, what must be the content of this inchoate science and its significance, as well as the lines along which it should develop."

Gulevich asserted that the comparative-evolutionary approach should be the guiding orientation of comparative biochemistry: "Biochemical studies of man must not be isolated from the corresponding studies of other classes of animals: in the study of his chemistry, man must not be separated from the rest of the tremendous and varied animal world. Just as comparative anatomy reveals an uninterrupted evolutionary chain from the simplest animals to man, so in biological chemistry it will be necessary to undertake a systematic study of the chemical statics and chemical dynamics of animal organisms on all zoological levels and to bind the study of man to comparative biological chemistry."

This was written long before the comparative biochemical studies by E. Baldwin (1938) and Florken (1941).

V. S. Gulevich indicated that phylogeny is organically connected with ontogeny. In the region of age-associated biochemistry, he pointed out a series of courses for investigation: embryochemistry, the chemical study of ontological development as the accelerated and shortened course of phylogenetic development, and the biochemistry of the child organism.

An extremely valuable contribution to the development of age-associated biochemistry was made by A. V. Palladin (starting in 1916) and his pupils. As early as the publication of his early monograph called "Study of the formation and isolation of creatine in animals" (1916), he reported a series of investigations connected with the age-associated characteristics of the organism. Later on, Palladin made a detailed study of the characteristics of creatine metabolism in children (1926–29) and then studied, in a number of papers, the changes in the creatine content at various ages and during the period of embryogenesis in a number of laboratory animals (1936–1938). In his subse-

quent works, Palladin made a detailed study of age-associated changes in a number of biochemical indices in mammalian tissues and at the same time conducted his investigations on a broad plane of comparative biochemistry.

Specifically, Palladin developed the biochemistry of the age-associated development of organisms and also concerned himself with the problems of the general theory of aging (1923).

Palladin has been studying very diligently the age-associated changes in the enzymatic properties of tissues and organs and the small details of the intermediate metabolism of proteins and carbohydrates. In recent years, the central orientation of Palladin's research has been the comparative biochemical study of the protein and nucleotide metabolism of the central nervous system. Particular attention has been paid to the age-linked biochemistry of the brain (and especially its embryochemistry). In Palladin's school of functional biochemistry of the brain, ontobiochemical investigations occupy an important place.

Among A. V. Palladin's pupils, who have done a great deal for the development of age-associated biochemistry, we must mention D. L. Ferdman, A. M. Utevskiy, L. I. Palladina, Ye. S. Savron', L. Ye. Rozenfeld', and many others.

The biochemistry and metabolic characteristics of childhood have been studied and are still being studied by O. P. Molchanova (1935-1948) and N. P. Tolkachevskaya (1939-1954). The latter, together with her co-workers, has made a particularly detailed investigation of gas exchange and protein and carbohydrate metabolism in young children.

Extensive investigations in the area of pediatrics, and particularly in the physiology of childhood, have been conducted in the laboratories of G. N. Speranskiy (1914-1945) and A. F. Tur (1927-1947). The work of V. G. Shtefko and his pupils (1924-1946) was devoted to the morphophysiology of early ontogenesis.

A great deal of work was done in the field of biochemistry of phylogenesis and ontogenesis of plants by A. B. Blagoveshchenskiy (1935). He believed that a tendency to cyclization, i.e., replacement of organic compounds with an open carbohydrate [tr.: sic] ring by compounds with a closed ring, is one of the basic mechanisms of both the phylogenesis and ontogenesis of plants. In this way, he formulated in a changed form the view of A. Pictet that in ontogenesis there is a gradual replacement of the more reactive and higher energy aliphatic compounds by less reactive and lower energy cyclic compounds. The age-associated cyclization of substances is one of the manifestations of an increase in entropic processes during the period of old age.

It must be noted that the theory of cyclization (as it was developed by A. Pictet) cannot be regarded as acceptable. A strong criticism of this theory was advanced by A. V. Nagorniy (1940): "Inasmuch as cyclic compounds contain less free energy than acyclic ones, the transformation of the latter into the former in closed systems is a natural spontaneous process. Since the living organism is an open system, subject to the unceasing processes of matter and energy metabolism, it is entirely clear that the processes of cyclization cannot be primary but are only a reflection of certain characteristics of the metabolism and subordinate to them.



"It is evident, therefore, that substances that exhibit the phenomena of cyclization and hysteresis in the living organism can do so only under conditions of total or partial preliminary loss of the ability to be metabolized.

"Thus, the theory of cyclization, which ignores metabolism, that fundamental quality of life, is entirely unacceptable from the methodologic viewpoint, as are in general all theories that attempt to understand individual evolution and its mechanisms from the viewpoint of the law of entropy" (A. V. Nagorniy, 1940).

The valuable experimental material obtained by A. V. Balgoveshenskiy retains its significance for the age-associated and evolutionary biochemistry of plants. Its interpretation must bear in mind the fact that the increase in cyclic compounds in the ontogenesis of plants is the result and not the cause of age-linked changes in metabolism. In addition to this, even in plants the relationships are far from being as simple as the cyclization theory would make them. As far as the animal organism is concerned, we find that the changes in the composition of the protoplasm that are actually observed are extremely complex and do not fit into the simplified schema of cyclization.

The problem of the age-associated development of plants was studied by N. P. Krenke (1933–1939) and his pupils (1933–1950). He advanced his theory of "cyclic aging and rejuvenescence" of plant organisms. In his fundamental monograph, which appeared posthumously (in 1940), he formulated the basic elements of his theory in the following manner:

"1. The individual inevitably grows old and dies.

"2. Aging, i.e., changes in the age-associated condition, does not usually agree with the calendar age of the individual.

"3. Aging, and hence the duration of life, are dependent on evolutionary factors but are greatly affected by the external conditions of development.

"4. All phenomena in the organism are connected to some extent with its age-associated state.

"5. Aging proceeds without interruption but not uniformly both for the individual as a whole in its various age-associated and phasic states and for the individual parts and signs of the individual.

"6. In the process of total individual aging, there is inevitably an uneven cyclic rejuvenescence in the neoformation of the living elements of the individual. But the absolute degree of this rejuvenescence progressively drops, i.e., aging is reflected in a progressive decrease of rejuvenescence.

"7. Rejuvenescence is the neoformation and development of young structures and substances and also the retardation of the aging of existing elements, but not a restoration of the past.

"8. The development of the organism is a struggle and unity of opposing processes in it: aging and rejuvenation.

"9. The age-associated condition of the parts of the individual is determined by the inherent and general age-associated state. The specific age-associated condition is the result of the processes that have gone on from the time of formation of the part in question, but these processes depend on the

general age-associated state of the individual as a whole up to the time of the formation of the part in question.

"10. The mechanism and intensity of the aging process differ in resting and in dividing cells."

Krenke was of the opinion that the slowest aging of all is exhibited by resting meristematic cells, which retain their capacity for energetic division. Among such tissue elements are the points of growth of sleeping and adventive [tr.: ?] buds and the growth points of germinating seeds. The aging process proceeds at the highest rate in "stormy" cell divisions.

"11. The age-associated variability has its regular morphologicphysiologic and biochemical expression, being characterized by curves with ascending and descending branches or with evident derivatives of these curves, i.e., on the ascending and descending branches, the development of aging is expressed—in general—in an opposite way."

Krenke made a sharp distinction between two concepts of age: inherent and general age and maturity. "The inherent age of a part of a plant is that time that has elapsed from the moment of its formation to the time under consideration, whereas the general age of this same part is determined by its inherent age and the age of the individual as a whole to the time of formation of the element in question.

"The term *maturity* is used to designate the actual vital capacity of the individual and its parts at the time under consideration, which is not usually fully correlated with their calendar age." He supports this position by the following example:

"As a rule, with the same inherent maturity, those simple organs or parts of them that possess a greater general maturity will be older. For example, month-old leaves of young tea or mulberry plants will be definitely younger than month-old leaves, developing under the same conditions, of old individuals of the same races of plants."

Krenke's theory has had a certain importance in selection (especially of perennial plants), in the multiplication of plants (especially vegetative), in plant surgery and phytopathology. It has doubtless enriched contemporary ideas about the very concept of age and the character of age-associated changes in plant organisms, i.e., in objects in relation to which these concepts are especially complex and least investigated. A plant is a much less "compact" and indivisible biological system than an animal. In the plant world, we find most strongly represented a "dismemberment" and a considerable independence of the parts of the organism. In addition to this, we find in plants the greatest contrasts in the duration of life: from several minutes or hours in primitive microscopic plants to several thousand years among the *Macrozamia*, in *Wellingtonia*, the yew, the oak, the baobab, the Lebanese cedar, the Australian eucalyptus, and the Mexican cypress.

The ontogenesis of plants is highly dependent on their passing through various states (the "staged" character of their development is very pronounced), and this also complicates the establishment of a unitary theory of their age-associated development.



It is natural that we will still need a prolonged development of plant physiology before we can establish the fundamental premises of a fully valid theory of the ontogenesis of the plant organism. Krenke's theory represents the first steps in this extremely important area. Some of his propositions are very questionable or obscure. Thus, it is difficult to agree with his reduction of the development of the organism to a struggle between aging and rejuvenescence, and hence with his reduction of the concept of vital capacity to the concept of maturity. The development of the organism proceeds in time and gives rise to extensive age-associated changes, but this development is certainly immeasurably richer in its differentiation, adaptation, and change in its interactions with external conditions than the inherent age-associated changes. Hence the vital potential of the organism also is not the consequence of its age alone, although it is indeed dependent on it to a considerable degree. Also questionable is his statement that the mechanism of aging differs in the resting and in the dividing cell. The tempos of aging may actually be different in them, but we cannot agree with the view that rapidly dividing tissue ages most rapidly of all. Thus, the vigorously dividing cells of the malpighian layer of the cutaneous epidermis, the intestinal epithelium, and the hemocytoblasts of the bone marrow in the higher vertebrates retain their viability to the greatest extent. The rate of division of cells is by no means always proportional to the rapidity of their differentiation.

In any case, N. P. Krenke's theory must be recognized as a serious attempt to develop a general theory of ontogenesis with respect to the peculiar conditions in the plant organism.

Proceeding from her ideas about the hemato-encephalic and histo-hematic barriers, L. S. Shtern (1935-1940) stressed the great importance of the age-associated consolidation of the colloids of these barriers and the resultant lowering of their permeability with the onset of old age. Both in the studies by her school and in a number of other investigations we find some evidence in support of such a reduction of permeability. Thus far, it is difficult for us to ascertain the actual significance of these still relatively unstudied changes in the total complex picture of aging of the organism as a whole.

O. B. Lepeshinskaya (1935-1953) regards aging as the consequence of the age-associated condensation of the colloids of the cell membranes. Age-associated condensation of the "superficial cortex" of the cytoplasm may be regarded as having been established in a number of cases. In addition to this, we must bear in mind the fact that the uninterrupted flow of the metabolism "sweeps away," after a few days or even hours, the molecules and their colloidal aggregates and does not give time for the appearance of hysteresis of the colloids (and especially of the proteins) in a pure form in the living protoplasm. Hence the condensation of the protoplasmic colloids is a consequence of the qualitative changes in protein metabolism with age.

A number of studies by V. A. Negovski and his pupils (1939-1954) have not dealt with the struggle against premature aging but rather with premature human death, occurring at a time when it is still possible for man, by making

use of his vital reserves, to save himself from death. This orientation is of considerable importance in the development of Russian thanatology and in general medical practice.

In 1945, a monograph appeared by Z. G. Frenkel' entitled "Prolongation of life and active old age." On the basis of a large amount of statistical material, this monograph sheds light on the problems of the social-economic prerequisites of longevity and of the preservation of good spirits and health even in extreme old age. Frenkel's characterizes the orientation of his investigations in the following fashion:

"Whereas other studies of old age and longevity usually take up and investigate from the biological viewpoint the nature and course of the aging processes in the organism, their physiology and pathology, I have set myself the task, in this book, of considering and clarifying the significance of the problem of old age in the total complex of the social-demographic problems that arise and develop in the course of the socialist reconstruction of society. My task is that of showing the social-economic and social-structural limits of the problem of the control of aging and of the mean life span. Achievement of this task is largely connected with an analysis and evaluation of statistical-demographic materials."

The creation of a new branch of physiological-biochemical science, namely, that of age-associated physiology and biochemistry, is inseparably linked with the scientific work of A. V. Nagorniy (1923-1953). In his investigations, he set himself the task of elevating the study of the problems of aging and longevity to the level of the establishment of a new branch of biological science, namely, ontophysiology, covering the mechanisms of the entire vital cycle of development of the whole animal organism, from its conception to its death.

Nagorniy's first theoretical study appeared as early as 1923: "Life, Old Age, and Death," and in 1934 he began his extensive experimental investigations, together with his pupils (I. N. Bulankin, V. N. Nikitin, A. A. Rubanovskiy, I. D. Shumenko, V. I. Makhin'ko, O. P. Silin, R. I. Golubistkaya, Ye. V. Parina, M. P. Kuznetsova, Ye. A. Sazonova, and others), for the purpose of making a systematic study of age-associated changes in higher animals. At the same time, many ideas were accumulated for the establishment of a future theory of ontogenesis.

Proceeding from the dialectic-materialistic representation of life as a continuous process beginning with the fertilization of the ovum and terminating with aging and death, Nagorniy formulated the subject and final objectives of age-associated physiology:

"Age-associated physiology is that science which studies the functional evolution of the individual vital process from its beginning and up to its natural end and has as its final task the discovery of the objective mechanisms that are fundamental to the individual life cycle" (1936). General and comparative physiology is organically linked to age-associated physiology, the initial principle of which is expressed in the following words of F. Engels: "A plant, an animal, every cell at every instant of its life is identical with itself and yet differs from itself as a result of its assimilation and excretion of substances, as a result of the



respiration, formation, and dying off of cells as a result of the continuing process of circulation, in a word, as a result of the sum of the continuous molecular changes that constitute life and whose total results appear before our eyes in the form of the vital phases: embryonic life, youth, sexual maturity, the process of multiplication, old age, and death."<sup>6</sup>

Regarding the organism as an integral system in which chemical, physical-chemical, functional, and structural characteristics and properties are mutually dependent on one another and indissolubly bound, forming a closed unity of chemistry, structure, and function, Nagorniy believed that the establishment of a complete theory of individual evolution is possible only on the basis of a detailed study of all these forms of appearance of vital activity in their age-associated evolution.

Nagorniy's ideas have confronted and are confronting age-associated physiology, biochemistry, and morphology with such major tasks as the following:

(a) the creation of a total picture of the age-associated changes in the biochemistry, structure, and functions of the animal organism that will cover fully and consecutively all the stages of its ontogenesis;

(b) the establishment of the major factors in the ontogenetic changes of the organism that determine the shifts in the stages of age-associated development from the stage of progressive growth to the stage of deep regression;

(c) on the basis of this, the discovery of ways to affect the ontogenesis of the animal organism and thereby effect a change in its nature in the direction of an increase in the duration of life and preservation of the vitality of the organism during the period of late ontogenesis;

(d) the creation of a valid and effective theory of the age-associated development of organisms, which will be of decisive importance in the search for ways of influencing the nature of organisms.

Nagorniy's laboratory performed some very important work on the age-associated changes in structure, the colloidal state, biochemistry, and physiological processes in higher animals. Particularly full studies were made of the biochemical features of the ontogenetic changes in the protein composition of protoplasm, linkages of proteins with nucleic acids and lipids, changes in the ratios of the fractions of nucleic acids (RNA and DNA), qualitative and quantitative changes in the nucleic acids (the ratios of pentoses and phosphorus in them), changes in the so-called structural proteins, the amino acid composition of proteins and of their various fractions, the colloidal-chemical stability and electrical charge of the protoplasmic proteins, and the enzymatic "spectra" of protoplasm.

A thorough study was made of the ontogenetic changes (in tissues and organs) of water, mineral substances, lipids, phosphatides and sterols, reserve alkalinity and pH, active acidity and buffer properties of the tissues, their reduction and oxidation potentials, electroconductivity, the energy of activation of enzymes and of the protein substrate, and many other matters.

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<sup>6</sup> F. Engels: *Dialectic of Nature*, Gospolitizdat, 1948, pp. 170-171.

Among the physiological indices of age-associated changes in tissues and organs, they investigated the changes in the total levels of the oxidative processes, tissue respiration, the activity of the individual enzymatic links in the oxidation-reduction process, glycolysis, the characteristics of energy, protein, carbohydrate, and mineral metabolism, the composition and properties of the urine, and so forth. A thorough investigation was made of the ontogenetic changes in the functional capacities of the entire organism and of its individual tissues and organs, the synthetic abilities of the organism, especially in connection with the synthesis of proteins, formation of ATP, and oxidative phosphorylation, synthesis of urea in the liver, protective syntheses, stimulation of tissue respiration in the whole organism by various factors, the ontogenesis of the reactivity of the organism to the introduction of a variety of hormones and the influence of loss (removal) of a number of glands of internal secretion on its metabolism at various ages, and many other matters. Studies were made of age-associated changes in biochemistry and functions of denervated organs, which provided a good deal of data for judging the ontogenetic evolution of the relations between the nervous system and the peripheral organs.

Nagorniy and his pupils also conducted extensive histochemical and micro-anatomical investigations, which provided a considerable amount of material for age-associated histophysiology.

All these investigations laid a broad experimental basis for recognition of the major features of the age-associated changes in the animal organism as a whole.

The following very important conclusions can be drawn from these studies.

1. The ontogenetic development of the organism from its beginning in the form of the fertilized ovum to its death does not by any means represent a fatal path of uninterrupted degradation of the colloidal state, biochemistry, physiological functions, and macro- and microstructures. The first early stages of ontogenesis are connected with an increase in many potentialities and in the activity of the protoplasm. Even in later ontogenesis, there are some high potentialities of vital activity, often found in a latent form.

2. The aging processes in the organism appear chiefly in the form of disturbances of synthesis, the assimilatory phase, which indicates the major significance of the changes in this phase ("synthetic, reactive nodes" of the protoplasm) in the processes of ontogenesis. Along with this, aging is accompanied by substantial changes in the processes of dissimilation and an impairment of the reciprocal "fit" of the processes of synthesis and breakdown.

3. The functional and biochemical evolution of organisms does not proceed uniformly in the various organs and tissues, also not uniformly with respect to the unity of the assimilatory and dissimilatory phases of the life process. With increasing age, there is an increase in the disharmony of the adjusted unity of the total animal organism.

4. With increasing age, the processes of synthesis become all the more "expensive" as regards energy. An increasingly small part of the organism's energy metabolism is used for the synthesis and resynthesis of the substances of the protoplasm.



5. The aging processes are connected with a "falling off" of the utilization of the energy of oxidational processes for the synthesis of macroergic systems of tissues, and the very consumption of the energy of the macroergs "falls off" with the processes of synthesis. As a result, there is a progressive decline of the synthetic potentialities of the organism with increasing age.

6. With increasing age, there is an increasing disharmony in the neurohormonal regulation of the vital processes and in the coordination and reciprocal "fit", dependent on this regulation, of the processes of the animal organism as a whole. There is a decline of the vitality of the neurohormonal regulation and a decrease of the ability of the tissues to respond to this action.

7. In ontogenesis, there is a progressive suppression of the capacity for restoration of the composition of the protoplasm of the organism to its full value, a decrease in autoregeneration of the protoplasm complex, which leads to irreversible changes in the composition of the entire organism and of its individual tissues and organs.

This last concept is based on the following extremely important statement by F. Engels: "Life is a method of existence of protein substances, and this method of existence consists essentially in a continuous renewal of the constituent chemical parts of these substances . . ."<sup>1</sup>

This autoregeneration of proteins (protoplasm) develops with age, and this development is not a simple restoration of that composition of the protoplasm which is characteristic of the preceding stage of ontogenesis. In addition, the age-associated development at the earliest stages is characterized by a capacity for autoregeneration such that the total biochemical and functional potential does not drop but, on the contrary, increases. Thus, in his work entitled "Characteristics of the individual evolution of the animal organism" (1947), Nagorniy wrote as follows: "The amount of energy evolved by a unit of live weight after fertilization of the ovum first increases, then reaches a certain maximum at an age that is fixed and characteristic for the species in question, and thereafter decreases during the entire rest of the animal's life. This pattern is characteristic not only of the whole organism but also of its parts taken individually: of its organs and tissues, and consequently, of living matter itself."

Some very interesting ideas are expressed by Nagorniy as to the significance of the progressive structuration of protoplasmic formations at the beginning of ontogenesis. He starts with the notion that structural and functional specialization of protoplasm, arising in the differentiation of cells and tissues, initially plays the role of heightening the vital potential. It increases the heterogenicity of the protoplasm, creates new colloidal surfaces, and intensifies the disequilibrium of the living matter as a whole.

"The resting ovum," writes Nagorniy, "exhibits an insignificant metabolism, and also, at the same time, apparently, an insignificant differentiation. The development of the ovum is also characterized by a heightened metabolism and an increased differentiation. This differentiation is multiple and varied;

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<sup>1</sup> F. Engels: *Anti-Duhring*, Gospolitizdat, 1948, pp. 77-78.

thanks to it, the organism in its various parts reveals physical, physical-chemical, and chemical heterogeneity, and also, consequently, a capacity for work and metabolism. It is entirely clear that prolonged preservation of these heterogeneities, essential for the realization of the vital process, requires a certain spatial localization and fixation of the heterogeneous parts, or in other words, morphological differentiation."

Nagorniy assigned a major role in the functional and structural specialization of the protoplasm to the metaplastm. In the later stages of ontogenesis, the activating role of the specialized formations and especially of the metaplastma is reduced and then is eliminated entirely, and phenomena of degradation make their appearance in the metaplastm. The tissues, overloaded by the metaplastm, lose their activating role, weaken, and grow old. Especially pronounced in this connection is their loss of their capacity for self-renewal.

Further investigations by pupils of A. V. Nagorniy showed (I. N. Bulankin, 1954; V. N. Nikitin, 1954) that differentiation leads to nucleoprotein depletion of the protoplasm and subsequent qualitative degradation of these nucleoproteins. Specifically, this can be one of the decisive conditions of the age-associated lowering of the synthesizing potentialities of the tissues.

Thus, Nagorniy removed aging from among the basic properties of life, from the contradictions inherent in the unity of life: "... because of causes that are to be found in the very essence of life, individual evolution, beginning with a marked predominance of the ascending processes, terminates with the victory of the descending processes. The contradiction that is the cause of the vital process is found, ultimately, to be also the cause of the negation of this life, the cause of the limitation of individual existence" (1940).

During the last years of his scientific creativity, Nagorniy advanced the concept of the nervous system as a factor that promotes longevity. He suggested that "the functions of the human cortex under certain conditions may be preserved without any appreciable weakening for an extremely long time, and in any case longer than the fully efficient activity of the other systems of the organism" (1954). He based this view on the remarkable statement by I. P. Pavlov:

"... Our nervous system is self-regulatory to the highest degree, and it is itself capable of self-improvement. One of the most important and strongest and most regular impressions that we obtain from studying higher nervous activity by our method is that of the extreme plasticity of this activity and of its tremendous capabilities: nothing remains fixed, and everything can be achieved or changed for the better, provided that suitable conditions exist."<sup>8</sup>

Developing this idea and applying it to the conditions of ontogenesis, Nagorniy writes as follows:

"No other part of the organism possesses these properties, this capacity for almost unlimited alteration. It may be said that all systems of the organism have 'lagged behind' the cortex of the cerebral hemispheres in their plasticity, and as a result of this it is completely conceivable that there are situations in

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<sup>8</sup> I. P. Pavlov: *Poln. sobr. trudov*. vol. III, 1st ed., 1949, p. 454.



which the cortex is not in a position to overcome the 'inertia' both of the other parts of the central nervous system subordinate to it and of the peripheral systems. It is easy to understand that as a result of this conflict, the preservation of the harmonicity of the whole becomes impracticable. This brings with it the heterochronicity of age-associated evolution in the various parts of the organism, and, as a finale, the picture of a vigorous mind in a helpless body, with the terminal victory of the latter over the former" (1954).

Nagorniy's ideas about the motive factors of ontogenesis represent the first draft of a major theory, the development of which, as he himself understood, required a great amount of subsequent work on the part of many research groups. It is natural that some elements of Nagorniy's teachings will be subjected to revision and amplification in this later work. Some weak aspects of Nagorniy's concepts are to be found in a certain overrating of the significance of the role of metaplasia as the underlying factor of age-associated changes in organisms and a certain one-sided evaluation of the significance of thermodynamic mechanisms in the development of the vital processes in ontogenesis. Aside from this, however, contemporary ontophysiology knows how much it owes to Nagorniy for his great contribution to the creation of this rapidly developing branch of biological science.

The future valid and complete theory of ontogenesis will doubtless take into consideration all the great advances that have been made in the field of age-associated physiology by many of its investigators. In the great outflow of creative thought, in the rapid replacement of the sometimes very contradictory and one-sided concepts of the age-associated development of the organism, it has gradually become possible to select and critically evaluate many important concepts and to enlarge them substantially. The individual elements of a full-valued theory of ontogenesis will doubtless contain the thoughts and discoveries of I. I. Mechnikov, M. S. Mil'man, A. A. Bogomolets, I. P. Pavlov, A. V. Palladin, N. P. Krenke, A. V. Nagorniy, and a whole pleiad of eminent Russian biologists and physicians.

In the present brief review of the history of Russian age-associated physiology, an effort has been made to present concisely the course of development of this outgrowth of science. This review has shown how much has already been accomplished in the creation of a fully satisfactory theory of ontogenesis and what have been the premises for the establishment of this Russian science. And it has also been made clear that much still remains to be done before we can accomplish the noble tasks of the remarkable science of the causes of the age-associated development of organisms and of ways of promoting longevity.

## IV. BIBLIOGRAPHIC SOURCES

At present, the problems of age-associated physiology, biochemistry, and morphology are being studied on a very large scale. We need only mention the fact that the bibliographic list published in the *Journal of Gerontology* (USA) last year contained 13,000 source references. In many countries, special journals are published that are devoted to the problems of aging, longevity, and ontophysiology (understood as the total study of the age-associated development of organisms). Among these, we should mention such journals as the following (the data in parentheses include the country and city where the journal is published and the year its publication started):

- (a) *Journal of Gerontology* (USA, St. Louis, 1946)
- (b) *Geriatrics* (USA, Minneapolis, 1946)
- (c) *Journal of American Geriatrics* (USA, Baltimore, 1953)
- (d) *Bulletin of the Institute of Gerontology* (USA, Iowa, 1954)
- (e) *Zeitschrift fur Alterforschung* (GDR, Dresden, 1938)
- (e) *Longevita* (Italy, Milan, 1952)
- (f) *Revista di Gerontologia e Geriatria* (Italy, Rome, 1956)
- (g) *Acta Gerontologica* (Italy, Milan, 1951)
- (h) *Giornale di Gerontologia* (Italy, Florence, 1953)
- (i) *Revue Francais de Gerintologie* (France, Paris, 1956)

There has been a widespread establishment of a variety of special societies and the convocation of annual international conferences and meetings on problems of age-associated physiology.

Unfortunately, bibliographic reviews of Russian ontophysiology and biochemistry are very rare and by no means reflect, to a sufficient extent, the great contributions of Russian scientists in this new and important branch of science. The review of work in this field written by A. V. Nagorniy (1938) is a very valuable one, but naturally it does not include the more recent studies. In 1951, there appeared a review of the literature entitled "Russian literature on age-associated changes in the metabolism and reactivity of the organism," by O. S. Shur'yan, I. V. Piskarskaya, and T. N. Stolyarova, in the proceedings of a conference at the Academy of Sciences, UkrSSR, devoted to these problems. Although this review covers only a part of the problems of age-associated physiology and pathology and even in these areas includes only some of the related material, it is of some scientific interest.

The present bibliography of Russian studies on ontophysiology is an attempt to fill the existing gap to some extent. Naturally, it has its flaws and has by no means succeeded in including all the older and newer studies. The author



would be very grateful for any advice as to the possibility of completing the list, filling its gaps, and correcting its inaccuracies. The list is given in alphabetic order. This has its drawbacks (e.g., as compared with a subject breakdown of the material), but also its advantages. The most important of its advantages is the fact that an alphabetic list provides an opportunity to collect in one place all the works of each of the investigators who have worked in the field of ontophysiology. In addition, this order facilitates greatly the finding of individual studies.

In pre-Revolutionary Russia, studies on age-associated physiology, biochemistry, and morphology appeared periodically in individual journals. Some of these journals are still being published. Up to 1917, periodical collections devoted to ontophysiological problems were extremely rare.

After October [tr.: i.e., the 1917 Revolution], there was a considerable increase in the number of studies on age-associated physiology. They are published in many journals, and many of these first appeared during this period. Scientific conferences on these problems are organized regularly, and the results reported therein appear in periodic collections and special publications. A series of outstanding monographs are being published on the problems of aging, promotion of longevity, age-associated physiology, biochemistry and morphology, and pediatrics.

The following list gives the names and years of publication of a number of the basic scientific journals that have published comprehensive bibliographies on these problems.

Vrach, St. P., 1880-1901

Prakticheskaya meditsina, St. P., 1885-1917; L., 1923-1928

Arkhiv biologicheskikh nauk, St. P., L., 1892-1917, from 1922

Russkiy vrach, St. P., P., 1902-1913

Populyarniy literaturno-meditsinskiy zhurnal d-ra Oksa, St. P., 1906-1916

Gigiyena i sanitariya, St. P., 1910-1913; M., 1933; 1936-1940; from 1943

Pediatrica, M., 1911-1914; 1924-1930, from 1937 and currently. It has been combined with a number of closely related journals:

(a) Zhurnal po izucheniyu rannego detskogo vozrasta, 1922-1931

(b) Okhrana zdorov'ya detey i podrostkov, 1931-1932

(c) Zhurnal po rannemu detskomu vozrastu, 1932-1933

Russkiy arkhiv anatomii, gistologii i embriologii, M.-L., 1916; 1924-1930

Profilakticheskaya meditsina, Kharkov, 1922-1937

Zhurnal teoreticheskoy i prakticheskoy meditsina, Baku, 1924-1930

Ukrainskiy medichni visti, Kiev, 1925-1931

Ukrainskiy medichniy arkhiv, Kharkov, 1927-1932

Ukrainskiy biokhimichniy zhurnal, Kiev, from 1928

Voprosy pediatrii i okhrana materinstva i detskva, L., from 1929

Vrachebnaya praktika, M., 1929-1930

Arkhiv anatomii, gistologii i embriologii, M.-L., from 1931

Medichniy zhurnal AN USSR, Kiev, from 1931

Voprosy pitaniya, Moscow, 1932-1941; 1948-1951; collections, since 1952

Uspekhi sovremennoy biologii, M., from 1932  
 Fiziologicheskoy zhurnal SSSR im. I. M. Sechenova, L., from 1932  
 Doklady AN. SSSR, Novaya seriya, M., from 1934  
 Akusherstvo i ginekologiya, M.-L., from 1936 and up to the present  
 Biokhimiya, M.-L., from 1936  
 Byulleten' eksperimentalnoy biologii i meditsiny, M., Medgiz from 1936  
 Tsentral'niy referativniy meditsinskiy zhurnal, M., 1936-1938; from 1929,  
 broken down into series  
 Pediatriya, akusherstvo, i ginekologiya, Kiev, from 1939  
 Profilaktichna meditsina, Kiev, from 1930  
 Zhurnal obshchey biologii, M., from 1940  
 Zhurnal vysshey nervnoy deyatel'nosti im. I. P. Pavlova, M.-L., from 1951

The number of Russian monographs and collections devoted to ontophysiological problems is so great that there is no possibility of reporting even the more important of them in the present paper. The best of them are the books by I. I. Mechnikov: "Studies of the Nature of Man" (1904) and "Studies of the Organism" (1907), and by A. V. Nagorniy "Problem of aging and longevity" (1940).

June 7, 1960. Paul DePorte, Translator.

Translated at the  
 National Institutes of Health, Bethesda, Md.



# RUSSIAN ALPHABET WITH TRANSLITERATION\*

(Same used for the Ukrainian)

А	а	а	Р	р	г
Б	б	б	С	с	в
В	в	в	Т	т	т
Г	г	г	У	у	а
Д	д	д	Ф	ф	г
Е	е	е	Х	х	kh
Ж	ж	zh	Ц	ц	ts
З	з	z	Ч	ч	ch
И	и	i	Ш	ш	sh
К	к	k	Щ	щ	shch
Л	л	l	Ъ	ъ	mute hard sign "
М	м	m	Ы	ы	y
Н	н	n	Ь	ь	mute soft sign '
О	о	o	Э	э	foreign e
П	п	p	Ю	ю	iu
			Я	я	ia

\* Applicable to bibliographical references from 287-on.

# Bibliography

[Items are alphabetized by their transliteration from the Russian—See page 42]

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